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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF PREVENTION, PESTICIDES AND TOXIC SUBSTANCES

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

MEMORANDUM

Date: October 16, 2008

SUBJECT: Permethrin: Estimated dermal absorption factor in human

PC Code: 109701
Decision No.: 363729
Petition No.: NA
Risk Assessment Type: NA
TXR No.: 0054971
MRID No.: 47514801

DP Barcode: D356089
Registration No.: NA
Regulatory Action: NA
Case No.: NA
CAS No.: 52645-53-1
40 CFR: NA

Ver.Apr.08

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Health Effects Division (7509P)
And
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Registration Division (7505P)

THROUGH: **Mary Manibusan, Acting Chief**
Toxicology and Epidemiology Branch
Health Effects Division (7509P)

TO: **Charles (Billy) Smith, Risk Assessor**
Reregistration Action Branch 2
Health Effects Division (7509P)
And
Jacqueline Guerry, Risk Manager Reviewer
Reregistration Branch 3,
Special Review and Reregistration Division (7508P)

I. CONCLUSIONS

The estimated *in vivo* human dermal absorption factors ranged from 1.4% to 5.7% using the rat and human *in vitro* dermal absorption data with the rat *in vivo* dermal absorption data. Based on the rat *in vivo* study, the increase in absorption at 120 hours indicated that radiolabel

Received 10/23/2008

(permethrin) remaining in the skin after washing at 24 hours was bioavailable. Therefore, **5.7% should be considered as the estimated human dermal absorption factor for risk assessment purpose.**

II. ACTION REQUESTED

The Special Review and Reregistration Division (SRRD) requested the Health Effects Division (HED) to review a study (MRID 47514801) submitted by the registrant to estimate dermal penetration of permethrin in human based on *in vitro* dermal penetration studies with rat and human skin and an *in vivo* dermal absorption study in rats.

III. BACKGROUND

Previously, the HED determined that a dermal absorption factor of 15% for permethrin should be used for the dermal part of the cancer equation for cancer risk assessment (TXR 0053385). The dermal absorption factor of 15% was estimated by dividing the LOAEL of the rat acute neurotoxicity study of 75 mg/kg/day and NOAEL of the 21-day dermal study of 500 mg/kg/day (the highest tested dose).

Later, the Registrant proposed to estimate human dermal absorption factor via a method referred to as a parallelogram (triple pack approach) by utilizing *in vitro/in vivo* dermal absorption data. The basic concept is that if the *in vivo* human and rat dermal absorption data is generated under the same conditions as the *in vitro* human and rat skin data, the ratio of dermal absorption factors (human skin/rat skin) measured *in vitro* will be the same as the ratio of dermal absorption factors (human/rat) measured *in vivo*. This estimation is based on a study design consists of at least three studies conducted using the same dose/duration regimen: (1) an *in vitro* study using human skin, (2) an *in vitro* study using rat skin, and (3) an *in vivo* rat dermal absorption study.

In 2007, a study protocol was submitted and accepted by the HED with a few modifications (TXR 0054683). The registrant proposed to generate a series of comparative *in vitro/ in vivo* dermal absorption studies consisting of three parts conducted using the same dose/duration regimen: 1) an in vitro study using human skin, 2) an *in vitro* study using rat skin, and 3) an *in vivo* dermal absorption study in rats.

In 2008, these studies were completed and submitted for Agency review. The submission is entitled "Estimated dermal penetration of permethrin in humans based on *in vitro* and *in vivo* data" (MRID 47514801).

IV. RESULTS/DISCUSSION

The Toxicology and Epidemiology Branch (TEB) has reviewed the study and considered the study as acceptable/non-guideline. This study is a combination of three parts (1) skin penetration of permethrin after topical application to excised rat and human skin, (2) skin penetration of permethrin after topical application to live rats, and (3) estimated dermal penetration of permethrin in humans based on *in vitro* and *in vivo* data.

1. *In vitro* studies in rat and human skins

The *in vitro* absorption of permethrin applied at three concentrations was relatively consistent within species (1-3% in humans and 18-24% in rats); indicating that absorption was not saturated at any of the applied concentrations in either species. In addition, absorption of permethrin was linearly distributed ($r^2 = 0.999$) for both species and was approximately 11-fold greater through rat skin than human. The greater concentration of radiolabel found in the dermis relative to the receptor fluid is consistent with the high lipophilic character of permethrin (LogP 6.50). The results obtained for the PBO control were consistent with previously published studies using human volunteers by Selim et al. (1999) and Wester et al. (1994).

2. *In vivo* studies in rats

The *in vivo* absorption of permethrin was relatively consistent at the three concentrations after 24 (22-28%) or 120 (30-38%) hours, indicating that absorption was not saturated at the highest dose. However, the slight increase in absorption at 120 hours is indicative that radiolabel remaining in the skin after washing at 24 hours was bioavailable. This is supported by the decrease in radiolabel at the application site 24 (13-22%) and 120 hours (1.9-2.3%) after application of the dose with a concomitant increase in the excreta from 24 hours (2.8-4.2%) or 120 hours (23-30%). Although permethrin is highly lipophilic, no significant accumulation was found in the carcass.

3. Estimated dermal penetration of permethrin in human

Using the above rat and human *in vitro* dermal absorption data with the rat *in vivo* dermal absorption data, an estimated human in vivo dermal absorption factor can be calculated with an equation: (human *in vitro*/rat *in vitro*) x rat in vivo = human *in vivo*. Estimated human dermal absorption factors of permethrin are as follows.

	Dermal absorption (% of application)			
	Permethrin ($\mu g/cm^2$)			PBO ($100\mu g/cm^2$)
	2.25	20	200	
Human/ *in vitro*	1.3	2.7	2.1	7.4
Rat/ *in vitro*	20	18	24	35
Rat/ *in vivo* (1 day)	22	22	28	NA
Rat/ *in vivo* (5 day)	38	38	30	42
Estimated Human/ *in vivo* (1 day)	**1.4**	**3.3**	**2.5**	NA
Estimated Human/ *in vivo* (5 day)	**2.5**	**5.7**	**2.7**	8.9

The estimated *in vivo* human dermal absorption factors ranged from 1.4% to 5.7%. Based on the rat *in vivo* study, the increase in absorption at 120 hours indicated that radiolabel (permethrin) remaining in the skin after washing at 24 hours was bioavailable. Also, the *in vivo* or *in vitro* absorption of permethrin was relatively consistent at all three doses. Therefore, 5.7% should be considered as the estimated human dermal absorption factor for risk assessment purpose.

DATA EVALUATION RECORD

PERMETHRIN
NON-GUIDELINE
STUDY TYPE: *IN VIVO* AND *IN VITRO* DERMAL PENETRATION – RAT and HUMAN
MRID 47514801

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
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Prepared by

Toxicology and Hazard Assessment Group
Life Sciences Division
Oak Ridge National Laboratory
Oak Ridge, TN 37831
Task Order No. 203-2008

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Disclaimer

This review may have been altered subsequent to the contractor's signatures above.

Oak Ridge National Laboratory managed and operated by UT-Battelle, LLC., for the U.S. Department of Energy under Contract No. DE-AC05-00OR22725.

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EPA Work Assignment Manager: Myron Ottley, Ph.D. **Signature:**
Registration Action Branch II, Health Effects Division (7509P) **Date:** 10/15/08

Template version 02/06

TXR#: 0054971

DATA EVALUATION RECORD

STUDY TYPE: *In Vivo* (Human and Rodent) and *In Vivo* (Rat) Dermal Penetration Study Non-Guideline

PC CODE: 109701 **DP BARCODE:** D356089

TEST MATERIAL (PURITY): Permethrin (cis/trans), (radiolabel purity = 99%; 44% cis/55% trans) (Unlabeled purity 97%; 43% cis/57% trans)

SYNONYMS: (+-)-3-Phenoxybenzyl 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane-carboxylate; cis, trans 3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylic acid (3-phenoxyphenyl)methyl ester.

CITATION: Ross, JH, Driver, JH, Reifenrath, W. (2008), Estimated dermal penetration of permethrin in humans based on *in vitro* and *in vivo data.* risksciences.net, LLC., Las Vegas, NV, Manassas, VA, Sacramento, CA (Study report authors). Report No. PDAG-001-08, August 18, 2008. MRID 47514801. Unpublished.

Reifenrath, W (2008). Skin penetration of permethrin after topical application to excised rat and human skin. Stratacor, Inc., 1315 S. 46th Street. Richmond, CA 94804. Study Report No. 95073, August 6, 2008. Included as an appendix to MRID 47514801. Unpublished. Conducted according to OECD 428 Guidelines.

Doherty, TV (2008). Skin penetration of permethrin after topical application to live rats. Stratacor, Inc., 1315 S. 46th Street. Richmond, CA 94804. Study Report No. 95074, August 6, 2008. Included as an appendix to MRID 47514801. Unpublished. Conducted according to OPPTS 870.7600 Guidelines.

SPONSOR: Consumer Specialty Products Assoc. Permethrin Dermal Absorption Group, 900 17th Street, Suite 300, Washington, DC 2006

EXECUTIVE SUMMARY:

In *in vivo* and *in vitro* dermal penetration studies (components of MRID 47514801), permethrin (radiolabeled purity = 99%, Lot/batch No 448-112-260) was applied to the dermal surface of groups of nine human skin samples/group, six rat skin samples/group, or the dorsal surface of 12

Sprague Dawley rats/group at concentrations of 2.25, 20, or 200 μg/cm^2 for 24 hours. For the *in vivo* study, half the rats in each group were sacrificed 24 hours after dermal application with the remainder sacrificed 120 hours after application. For quality control purpose, piperonyl butoxide (100 μg/cm$^{2)}$ was included to both studies because results of dermal penetration on piperonyl butoxide are well documented in rat and human skin models.

The overall recovery of the radiolabeled permethrin was good to excellent in both studies; being >96% for the *in vitro* rat and human studies and 85% for the *in vivo* rat study. Dermal penetration and absorption of radiolabeled permethrin were consistent between the two types of experiments with rats being ~21% for the *in vitro* and *in vivo* studies. For the *in vitro* study, the absorption of permethrin applied at three concentrations was relatively consistent within species (1-3% in humans and 18-24% in rats); indicating that absorption was not saturated at any of the applied concentrations in either species. In addition, absorption of permethrin was linearly distributed ($r^2 = 0.999$) for both species and was approximately 11-fold greater through rat skin than human. For the *in vivo* study, permethrin absorption was relatively consistent at the three concentrations after 24 (22-28%) or 120 (30-38%) hours, again indicating that absorption was not saturated at the highest dose. However, the slight increase in absorption at 120 hours is indicative that radiolabel remaining in the skin after washing at 24 hours was bioavailable. This is supported by the decrease in radiolabel at the application site from 24 (13-22%) to 120 hours (1.9-2.3%) hours after application of the dose with a concomitant increase in the excreta from 24 hours (2.8-4.2%) to 120 hours (23-30%). Although permethrin is highly lipophilic (LogP = 6.50), no significant accumulation was found in the residual carcass. Permethrin was readily excreted with most occurring within 48 hours of application. The amount excreted in the urine was approximately three-fold greater than that found in the feces at 24 and 120 hours after application.

These dermal penetration studies with in vitro rat and human skins and in vivo live rats are considered **Acceptable.** They were done according to applicable guidelines; OPPTS 870.7600 and OECD 428.

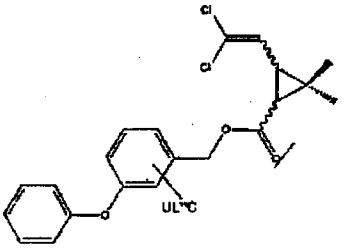
COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS:

A. MATERIALS:

1. Test material: Permethrin (radiolabeled)

Description: Not reported
Lot/batch #: 448-112-260
Purity: 99.1% a.i. (44% cis/55% trans)
Compound stability: Duration of study
CAS # for TGAI: 52645-53-1
Structure:



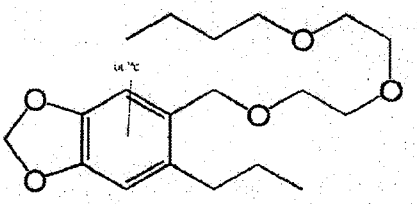
Radiolabeling: Universal on benzyl ring-^{14}C, cis-, trans-
Vehicle/Solvent used: Ethanol
Specific Activity: 260 mCi/mmol (1 mCi/mL)
Source: Moravek Biochemicals, Inc.

Unlabelled Test Material: Permethrin

Purity: 97% (43% cis/57% trans)
Lot/batch #: VTC-1066-33A
Source: Valent Biosciences Center
Description: Crystalline solid
Expiration date: May 16, 2009

Reference Material Piperonyl butoxide (radiolabeled)

Purity: 99.5%
Lot/Batch #: 176-122-0365
Source: Moravek Biochemicals, Inc.
CAS # 51-03-6
Radiolabeling: Universal on phenyl ring-^{14}C
Specific Activity: 36.5 mCi/mmol
Structure:



Unlabeled Reference Material: Piperonyl butoxide

Purity: 98%
Source: Chem Service, Inc.
Lot/Batch #: 390-71A
Expiration date: October, 2009

2. Test Specimens (*in vitro* study):

Human skin preparations: Freshly excised human skin samples obtained from the abdomen by plastic surgery that composed of the epidermis and the outer-most portion of the dermis containing the papillary dermis were cut into thicknesses ranging from 250 – 750[1] µm. Thirty-six skin samples were selected from three different donors (12/donor) to provide nine replicates for each concentration of the test material plus the radiolabeled piperonyl butoxide (PBO) control.

Rat skin preparations: Fresh rat skin preparations were cut into thicknesses of 200 – 350 µm to provide 24 skin samples from six different rats (four replicates/rat) for each concentration of test material plus the PBO control. The strain of rat used for the skin preparations was not reported were excised.

3. Test animals (*in vivo* study):

Species:	Rat	
Strain:	Sprague Dawley	
Age/weight at study initiation:	Approximately 9 weeks; males - 255.1-297.4 g	
Source:	Charles River Laboratories, Wilmington, MA	
Housing:	Individually in polycarbonate metabolism cages	
Diet:	Harlan Teklad Certified Rodent Diet 8728C, *ad libitum*	
Water:	Source not reported, *ad libitum*	
Environmental conditions:	**Temperature:**	18 - 26°C
	Humidity:	50 ± 20%
	Air changes:	Not reported
	Photoperiod:	12 hrs light/dark
Acclimation period:	≥ 5 days	

B. STUDY DESIGN:

1. Dose:

Rationale: The doses for the *in vitro* (human and rat skin preparations) and *in* vivo (rat) studies approximate the range of exposures expected in residential and worker settings.

Nominal doses: The nominal doses for all studies were 2.25, 20, or 200 µg/cm^2 skin for permethrin and 100 µg/cm^2 skin for PBO.

Actual doses: Since the exposed skin area was 0.8 cm^2 for the *in vitro* human and rat skin

[1] The skin thickness of several samples were exceeded the specified in the protocol at 250-350 µm. The study report stated that while the thickness of the dermis may affect the proportion of penetrant that travels into the receptor fluid, the inclusion of dermal residues of penetrant, along with receptor fluid levels, will take this effect into account. In addition, a tritium test with varies skin thickness did not show statistically significant correlation between percent absorption and skin thickness of different samples used in this study.

preparations, the actual dose applied was 1.8, 16, or 160 µg of permethrin and 80 µg of PBO. The applied dose was as reported for the *in vivo* study.

Dose volume: The application volume for all in vitro studies was 5 µL which was applied with a blunt-tipped Hamilton syringe. For the in vivo studies, 25 µL of the prepared permethrin or PBO dose solution was applied to 4 cm^2 skin. The amount of applied radioactivity was ~1.2 µCi/permethrin or PBO/cm^2 for the *in vitro* and *in vivo* studies.

Duration of exposures: ***In vitro***: The time-course of dermal penetration was followed over 24 hours from samples collected from the tissue culture medium in the penetration chamber at 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, and 24 hours after sample application. ***In vivo***: The skin of all rats was washed 24 hours after sample application. Half the rats in each permethrin group were sacrificed 24 hours after dermal application while the remainders were sacrificed after 120 hours.

Termination periods (time from dose to sacrifice): ***In vitro*:** The *in vitro* study was terminated 24 hours after sample application. ***In vivo***: Half of the permethrin treated rats (6 rats/group) were terminated 24 hours after sample application while the remainder and the PBO treated rats were terminated 120 hours after sample application.

Number of animals or samples/group: ***In vitro studies*:** Thirty-six human skin samples from three donors were used that provided nine replicates for each of the permethrin concentrations (2.25, 20, or 200 µg/cm^2 skin) and the PBO control (100 µg/cm^2 skin). Twenty-four rat skin samples from six different rats were used for each of the permethrin concentrations (2.25, 20, or 200 µg/cm^2 skin) and the PBO control (100 µg/cm^2 skin). ***In vivo* studies**: Twelve rats/group were dermally exposed to 2.25, 20, or 200 µg permethrin/cm^2 skin and six rats were dermally exposed to 100 µg PBO/cm^2 skin.

2. **Specimen or Animal preparation**: ***In vitro studies*:** The chambers used for the *in vitro* studies were composed of a glass upper donor chamber clamped to a stainless steel lower penetration chamber. After preparation of the skin specimens, they were mounted on the penetration cell with the dorsal surface exposed to the atmosphere while the ventral surface was in contact with tissue culture medium (not further described). Previous studies had shown that the skin samples prepared and used as described maintain viability for 50 hours after collection. The actual exposure area for each skin tissue was 0.8 cm^2.

***In vivo* studies:** Shortly before treatment, the rats were lightly anesthetized and area of skin on the mid-dorsal trunk was shaved. A 4 cm^2 area was drawn within the shaved area with an indelible ink. Prior to application of the test sample, a protective patch to cover the application site was prepared by cutting a 3 cm^2 by 0.4 cm thick foam pad with a 2.5 cm diameter hole punched in the middle. Nylon screen was glued on the outer side of the hole, and a layer of surgical gauze was place over the screen. After application of the test material to the center of the shaved area, the site was allowed to dry and the protective, non-occlusive patch was applied to surround, but not touch, the treated skin. The patch was secured to the

treatment site with surgical tape in such a manner as to not occlude the application site.

3. **Dose preparation, administration and quantification:**

Preparation: All permethrin dose solutions were prepared in ethanol while the PBO dose solution was prepared in isopropanol by combing sufficient amounts of radiolabeled and non-radiolabeled test material. All dosing solutions were prepared to provide ~1.2 μCi/cm^2 treated area. The time interval between dose solution preparation and application was not located in the study reports.

Application: For the *in vitro* studies, 5 μL of the dosing solution was applied with a blunt-tipped Hamilton syringe and spread evenly across the surface of the skin. The solvent was allowed to evaporate from the application and the site was not covered. For the *in* vivo study, 25 μL of the prepared dosing solutions was spread evenly over the application area, the solvent allowed to evaporate, and the site covered with a protective, non-occlusive patch prepared as described above. The treated rats were placed into individual polycarbonate metabolism cages for the remainder of the in-life stage of the study. CO_2 was not collected from the rats.

Quantification: *In vitro* studies: Radioactivity (dpm) and radiochemical purity of the dosing solutions were determined prior to dosing. The radiometric assays were done with a temperature controlled liquid scintillation counter equipped with a static controller and luminescence correction. Unquenched reference standards and ^{14}C quench standards were used. At the end of the study, the human skin surface application areas were removed from the penetration chambers, pinned on cork boards overlain with plastic sheeting, and decontaminated successsively with three cotton wipes containing liquid ivory soap, three cotton wipes containing distilled water, and the surface area dried with two cotton wipes. The skin surface was further decontaminated with two tape strips. The cotton wipes and tape strips were placed in separate LSC vials containing scintillation fluid for counting. The skin was removed from the diffusion cells and the epidermis covered with a polyvinyl film. A brass weight heated to 65°C was pressed against the epidermis for 90 seconds. The epidermis was then teased from the dermis with forceps. The epidermis and dermis were placed in separate LSC vials and solubilized with tissue solubilzer at 50-60 °C for one hour. Ten ml of scintillation fluid was added to each vial before determination of radioactivity. Radioactivity was also determined on the polyvinyl film and plastic underlying film used for sample preparation. For rat skin, the epidermis was peeled from the underlying dermis using forceps. The epidermis, dermis, and underlying film were processed as described for human skin. Samples of the tissue culture fluid collected during the study were added to LSC fluid for radiometric analysis. Radiochemical purity assays were done by HPLC equipped with radiometric detection.

***In vivo* studies:** Radioactivity for the *in* vivo study was determined on equipment similar to that described for the *in vitro* studies. Samples of dose controls, ethanol dressing extracts, urine, and decontamination wipes were placed in LSC vials and counted after the addition of

scintillation fluid. Tape strips were dissolved in 1-2 mL tetrahydrofuran before addition to scintillate and counting. A sample oxidizer was used to convert radioactive residues in application site skin, carcass, and feces to $^{14}CO_2$ which was trapped in Carbosorb and counted in scintillation fluid. For fecal samples, an equal volume of cellulose powder and 200 µL accelerant were added prior to combustion. Background for all counts was automatically subtracted and dpm determined by Automatic External Standards.

For both types of studies, the limit of detection was ~two times background (22 dpm above background).

4. **Skin wash: *In* vitro studies:** Twenty-four hours after application, the human skin surface application areas were removed from the penetration chambers, pinned on cork boards overlain with plastic sheeting, and decontaminated successively with three cotton wipes containing liquid ivory soap, three cotton wipes containing distilled water, and the surface area dried with two cotton wipes. The skin surface was further decontaminated with two tape strips. In the case of rat skin, the decontamination procedures used for human skin caused separation of the epidermis from the dermis of the split-thickness preparations. In this case, skin decontamination was effected by teasing the epidermis away from the dermis with forceps. Since dermal residues represent compound available for absorption, the amount of radiolabel found in the dermis was added to the total amount found in the receptor fluid to provide an estimate of absorption.

   ***In vivo* studies:** Twenty-four or 120 hours after application, the rats were euthanized. The application site was decontaminated with three cotton balls dampened with a liquid Ivory soap solution, three cotton balls dampened with distilled water, and two dry cotton balls. All cotton balls were retained for determination of radioactivity. The skin at the application site was excised, and the remaining carcass was cut into small pieces, plunged in liquid nitrogen, and blended in a high-speed blender.

5. **Sample collection: *In vitro* studies:** Samples of the tissue culture fluid in the penetration chamber were collected 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, and 24 hours after sample application. Aliquots of each sample were placed in LSC and the radioactivity determined.

   ***In vivo* studies:** Urine and feces were collected at 12 hour intervals from all rats included in the study. Half of the permethrin treated rats (6 rats/group) were terminated 24 hours after sample application while the remainder (six rats/group) and the PBO treated rats (six rats) were terminated 120 hours after sample application.

II. RESULTS:

A. SIGNS AND SYMPTOMS OF TOXICITY:

No clinical signs of toxicity were reported for the *in vivo* rat study.

B. *IN VITRO* STUDIES:

As shown in Table 1, recovery of the radiolabel was excellent for all concentrations and both test materials in both species (>96% for humans and rats). The absorption of permethrin applied at three concentrations was relatively consistent within species (1-3% in humans and 18-24% in rats); indicating that absorption was not saturated at any of the applied concentrations in either species. In addition, absorption of permethrin was linearly distributed ($r^2 = 0.999$) for both species and was approximately 11-fold greater through rat skin than human. The greater concentration of radiolabel found in the dermis relative to the receptor fluid is consistent with the high lipophilic character of permethrin (LogP 6.50). The results obtained for the PBO control were consistent with previously published studies using human volunteers by Selim et al. (1999) and Wester et al. (1994).

Table 1. Average disposition of radioactivity (percent of applied radioactive dose) following topical application of radiolabeled permethrin or PBO to excised human and rat skin samples.

Compartment	Permethrin (µg/cm^2)			PBO (µg/cm^2)
	2.25	20	200	100
Human				
Skin Decontamination	85 ± 6	79 ± 9	79 ± 7	72 ± 12
Epidermis	3.1 ± 1.1	3.8 ± 1.6	2.0 ± 1.1	4.1 ± 1.8
Dermis	1.1 ± 1.1	2.5 ± 3.7	2.0 ± 1.7	5.5 ± 5.9
Receptor Fluid	0.23 ± 0.10	0.20 ± 0.09	0.10 ± 0.04	1.9 ± 0.8
Total Recovery	97 ± 1	96 ± 2	96 ± 3	96 ± 4
Percutaneous Absorption[1]	1.3 ± 1.1 (0.023 ± 0.020)[2]	2.7 ± 3.6 (0.43 ± 0.58)	2.1 ± 1.7 (3.4 ± 2.7)	7.4 ± 5.4 (5.9 ± 4.3)
Rat				
Skin Decontamination	N/A	N/A	N/A	N/A
Epidermis	72 ± 9	72 ± 4	67 ± 10	58 ± 9
Dermis	15 ± 9	14 ± 4	21 ± 8	21 ± 11
Receptor Fluid	4 ± 1	4.1 ± 0.8	2.5 ± 0.4	14 ± 4
Total Recovery	97 ± 1	96 ± 1	97 ± 1	99 ± 1
Percutaneous Absorption[1]	20 ± 9 (0.36 ± 0.16)[2]	18 ± 5 (2.9 ± 0.8)	24 ± 8 (38 ± 13)	35 ± 7 (28 ± 7)
Ratio (human/rat)	15.4	6.7	11.4	4.7

Data from Tables 1 - 4, pages 49 and 50 of MRID 47514801
[1]Receptor fluid + dermis
[2]Results in parentheses are mass equivalents (µg) of radiolabel
N=9 for human and N=6 for rat skin samples.
N/A = Not applicable

IN VIVO STUDIES:

As shown in Table 2, overall recovery of the radiolabel was good, ranging from 85-90% of the applied dose for all concentrations 24 or 120 hours after application. The absorption of permethrin was relatively consistent at the three concentrations after 24 (22-28%) or 120 (30-38%) hours, indicating that absorption was not saturated at the highest dose. However, the slight increase in absorption at 120 hours is indicative that radiolabel remaining in the skin after washing at 24 hours was bioavailable. This is supported by the decrease in radiolabel at the application site 24 (13-22%) and 120 hours (1.9-2.3%) after application of the dose with a

concomitant increase in the excreta from 24 hours (2.8-4.2%) or 120 hours (23-30%). Although permethrin is highly lipophilic, no significant accumulation was found in the carcass.

Table 3 shows that permethrin was readily excreted with most occurring within 48 hours of application. The amount excreted in the urine was approximately three-fold greater than that found in the feces and the dose of permethrin did not seem to affect the route of elimination.

Table 2. Disposition of radioactivity (percent of applied radioactive dose) 24 hours and 120 hours after topical application of permethrin or PBO to male rats.

Compartment	Permethrin (µg/cm^2)			PBO (µg/cm^2)
	2.25	20	200	100
24 Hours				
Dressing	49 ± 17	50 ± 13	43 ± 10	N/A
Skin Decontamination	16 ± 9	17 ± 9	17 ± 6	N/A
Tape Strip	2.3 ± 1.3	2.8 ± 1.3	4.9 ± 2.5	N/A
Application Site Skin	13 ± 4	15 ± 7	22 ± 7	N/A
Carcass	1.7 ± 0.7	1.3 ± 0.6	1.3 ± 0.3	N/A
Urine	3.9 ± 2.2	3.3 ± 1.4	2.7 ± 0.9	N/A
Feces	0.3 ± 0.3	0.3 ± 0.3	0.12 ± 0.07	N/A
Total Recovery	86 ± 5	89 ± 5	90 ± 7	N/A
Percutaneous Absorption[1]	19 ± 7 (2.1 ± 0.8)[2]	20 ± 8 (20 ± 8)	26 ± 8 (260 ± 80)	N/A
Absorption Normalized to Recovery (100%)	22 ± 8	22 ± 9	28 ± 7	N/A
120 Hours				
Dressing	34 ± 7	38 ± 20	15 ± 15	34 ± 8
Skin Decontamination	18 ± 5	15 ± 6	14 ± 5	17 ± 7
Tape Strip	1.6 ± 0.6	1.2 ± 0.4	2.4 ± 1.2	1.1 ± 0.5
Application Site Skin	2.2 ± 1.4	1.9 ± 1.4	2.3 ± 1.7	1.0 ± 0.8
Carcass	1.8 ± 0.8	1.4 ± 0.6	1.2 ± 0.6	4.4 ± 0.9
Urine	20 ± 3	22 ± 9	17 ± 7	13 ± 1
Feces	8 ± 3	8 ± 5	6 ± 2	19 ± 3
Total Recovery	85 ± 3	87 ± 2	88 ± 2	90 ± 4
Percutaneous Absorption[1]	32 ± 5 (3.6 ± 0.6)[2]	33 ± 15 (33 ± 15)	27 ± 12 (270 ± 120)	38 ± 3 (190+15)
Absorption Normalized to Recovery (100%)	38 ± 5	38 ± 17	30 ± 13	42 ± 3

Data from Tables 1 and 2, pages 227-228 of MRID 47514801
[1]Urine + feces + application site skin + carcass
[2]Results in parentheses are mass equivalents (µg) of radiolabel
N=6 for all groups
N/A = Not applicable

Table 3. Excretion of radiolabel (percent of dose) five days following topical application of ^{14}C-permetrhin or ^{14}C-PBO			
Time (hours)	**Urine**	Feces	Urine + Feces
2.25 µg permethrin/cm^2			
24	3.69	0.54	4.23
48	8.87	2.50	11.37
72	4.43	3.29	7.72
96	1.98	1.32	3.30
120	1.07	0.66	1.73
Total	20.04	8.31	28.35
20 µg permethrin/cm^2			
24	4.51	0.51	4.82
48	9.61	3.75	13.36
72	4.63	2.40	7.03
96	1.82	1.10	2.92
120	1.16	0.65	1.81
Total	21.73	8.21	29.94
200 µg permethrin/cm^2			
24	2.47	0.17	2.64
48	7.94	2.22	10.16
72	3.84	1.90	5.74
96	1.90	1.02	2.92
120	1.15	0.62	1.77
Total	17.30	5.93	23.23
100 µg PBO/cm^2			
24	3.81	1.96	5.77
48	4.59	6.84	11.43
72	2.51	3.57	6.08
96	1.53	4.34	5.87
120	0.96	2.48	3.44
Total	13.40	19.19	32.59

Data from Tables 6-9 on page 232 of MRID 47514801

III. DISCUSSION AND CONCLUSIONS:

A. REVIEWER COMMENTS:

Well conducted *in vitro* studies on rat and human skin and rat *in vivo* dermal penetration were done on three concentrations of permethrin, 2.25, 20, and 200 µg/cm^2, to determine the difference between rat and human absorption. The results of both studies utilized 100 µg/cm^2 PBO to compare the results to well-documented prior studies with the compound.

The overall recovery of the radiolabeled permethrin was good to excellent; being >96% in the *in vitro* rat and human studies and 85% in the *in vivo* rat study. Dermal penetration and absorption of radiolabeled permethrin were consistent between the two types of studies for rat; being ~ 21% for the *in* vitro and *in* vivo studies. For the *in vitro* study, the absorption of permethrin applied at three concentrations was relatively consistent within species (1-3% in humans and 18-24% in rats); indicating that absorption was not saturated at any of the applied concentrations in either species. In addition, absorption of permethrin was linearly

distributed ($r^2 = 0.999$) for both species and was approximately 11-fold greater through rat skin than human.

For the *in vivo* study, the absorption of permethrin was relatively consistent at the three concentrations after 24 (22-28%) or 120 (30-38%) hours, again indicating that absorption was not saturated at the highest dose. However, the slight increase in absorption at 120 hours is indicative that radiolabel remaining in the skin after washing at 24 hours was bioavailable. This is supported by the decrease in radiolabel at the application site 24 (13-22%) and 120 (1.9-2.3%) hours after application of the dose with a concomitant increase in the excreta from 24 hours (2.8-4.2%) to 120 hours (23-30%). Although permethrin is highly lipophilic (LogP = 6.50), no significant accumulation was found in the residual carcass. Permerthrin was readily excreted with most occurring within 48 hours of application. The amount excreted in the urine was approximately three-fold greater than that found in the feces. The dose of permethrin did not seem to affect the route of elimination.

B. STUDY DEFICIENCIES:

None that would influence interpretation of the results.

IV. REFERENCES

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